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EXAMINER	
SAJJADI, FEREYDOUN GHOTB	
ART UNIT	**PAPER NUMBER**
1633	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/500,521	SCHREIBER, GIDEON	
	Examiner	Art Unit	
	FEREYDOUN G. SAJJADI	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *62,66-71,75-82 and 87-93* is/are pending in the application.

4a) Of the above claim(s) *87 and 90-92* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *62, 66-71,75-82,88,89 and 93* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Request for Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 8, 2008 that includes a response to the office action dated January 8, 2008, has been entered. Claims 62, 66-71, 75-82 and 87-93 are pending in the application. Claim 62 has been amended. No claims were cancelled or newly added. Claims 87 and 90-92 stand withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144). See MPEP § 821.01.

Claim 1 has been examined commensurate in scope with the elected mutations of alanine at positions 78 and 100 of SEQ ID NO: 2. Claims 88 and 89 have been examined to the extent that they embrace the elected species of multiple sclerosis as an autoimmune disease and a method of administering to a patient a therapeutically effective amount of a composition comprising the polypeptide of SEQ ID NO: 2; or said composition further comprising an IFN antagonist.

Claims 62, 66-71, 75-82, 88, 89 and 93 are under current examination.

Response to Claim Rejections - 35 USC § 112-Scope of Enablement

Claims 62, 66-71, 75-82 and 93 stand rejected under 35 U.S.C. §112, first paragraph, for lacking an enablement for the full scope of the invention. The rejection set forth on pp. 6-7 of the office action dated July 26, 2006, pp. 3-5 of the office action dated July 2, 2007, and pp. 2-4 of the previous office action dated January 8, 2008 is maintained, for reasons of record.

The previous office actions indicated that the specification is only enabling for an isolated human IFNAR2- EC polypeptide, wherein amino acid residues His 78 and Asp 100 of the extracellular domain are substituted by alanine, as set forth in SEQ ID NO: 2.

Applicant disagrees with the rejection, arguing SEQ ID NO: 2 represents the amino acid sequence of the extracellular domain of IFNAR2 and contains alanine substitutions at positions 78 and 100, and is demonstrated as a working embodiment, to exhibit synergistically increased affinity for IFN-β. A polypeptide comprising SEQ ID NO: 2, as claimed, necessarily comprises the sequence demonstrated by the instant specification to exhibit increased affinity for IFN- β. Accordingly, the pending claims encompass "other type I IFN receptors" only to the extent that such receptors comprise SEQ ID NO: 2. The Examiner has simply not provided any basis for concluding that such receptors "do not retain the synergistic increase in affinity for IFN- β." Further arguing that the Examiner has improperly read this limitation out of the claim, and one of ordinary skill in the art would, in view of the disclosure provided by the instant Application, and of common general knowledge at the time the present Application was filed, make the claimed polypeptides and identify those polypeptides which exhibit the claimed synergistically enhanced affinity for IFN- β without recourse to undo experimentation. Applicant's arguments have been fully considered, but are not found persuasive.

In response, it should be noted that the limitation pertaining to synergistic increase in affinity for IFN- β has not been read out of the claim, as it forms the key issue for the instant ground of rejection. As previously indicated, page 1, paragrpah [0003] of the the amended specification states: type I interferons include interferon α, interferon β and interferon ω, while type II interferon includes interferon γ. IFNAR 2 is the beta subunit or beta chain of the type I IFN receptors (p. 2, paragraph [0006], and as the polypeptide claimed in claim 62 comprises the sequence of SEQ ID NO: 2, other type I IFN receptors cannot be excluded, and hence the claims encompass polypeptide sequences of numerous receptor variants of the type I IFN receptors, such as membrane bound, cytoplasmic or soluble forms. Therefore, while the enabled scope may not extend to polypeptides which do not retain the synergistic increase in affinity for IFN-β, the broadly claimed scope clearly does, and thus highlights the enablement issue. Moreover, the

claims allow for the addition of any of numerous amino acid to various regions of SEQ ID NO: 2 that can introduce substantial variation, affecting binding of IFNβ.

As previously indicated, Bowie, et al. (Science, 247: 1306-10, 1990; or record) provide notable insight into the lack of reasonable predictability for the mutation of any particular protein. Bowie state that while many substitutions may be tolerated, in other cases substitutions may not be tolerated at all (e.g., 1306, col. 2, paragraph 2). Moreover, the significance of surface and buried amino acids while is not reasonably predictable either (pp. 1306-07), surface sites may not have any importance, but sometimes they are absolutely important due to binding (p. 1308), and predicting structure with reasonable predictability is generally limited to homologous proteins, but even that is difficult due to alignment problems (p. 1308). Bowie continues: it is not reasonably predictable that any particular amino acid change, deletion, or addition would provide a functional molecule with similar activity, and only painstaking analysis would provide such information for any particular change (e.g., pp. 1309-10). Therefore, it remains unknown whether the mutations of his 78 and asp 100 in SEQ ID NO: 2 would retain their synergistic increase in binding IFNβ, following a fusion to any of numerous unknown amino acid sequences of unlimited size, that can introduce substantial variation, affecting binding of IFNβ. It should additionally be noted that as Applicants have demonstrated in the disclosure, alteration of only two amino acids in SEQ ID NO: 1 result in significant alteration in the affinity of the extracellular receptor for IFNβ. Therefore, it is reasonable to assume that further conformational changes in the protein's structure would also alter the affinity of the extracellular receptor for IFNβ. What is not known however, is whether such alterations would retain the synergistically increased affinity of SEQ ID NO: 2 for IFNβ. As the outcome of such analysis for the numerous fusion proteins embraced by the instant claims is unpredictable, additional experimentation involved in determining embodiments that may be operative on the part of the skilled artisan is considered undue. A single embodiment may provide broad enablement in cases involving predictable factors, such as mechanical or electrical elements. *In re Vickers*, 141 F.2d 522, 526-27, 61 USPQ 122, 127 (CCPA 1944); *In re Cook*, 439 F.2d 730, 734, 169 USPQ 298, 301 (CCPA 1971). However, in applications directed to inventions in arts where the results are

unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. *In re Soll*, 97 F.2d 623, 624, 38 USPQ 189, 191 (CCPA 1938).

Thus, the rejection of claims 62, 66-71, 75-82 and 93 is maintained for reasons of record and the foregoing discussion.

Response to Claim Rejections - 35 USC § 112-Lack of Enablement

Claims 88 and 89 stand rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. The rejection set forth on pp. 5-7 of the office action dated July 2, 2007, and pp. 4-5 of the previous office action dated January 8, 2008 is maintained, for reasons of record.

Applicant traverses the rejection, and with reference to the teachings of the prior art, argue that the activity of type I interferons in modulating the immune system was known and it was known that type I interferons act through a cell surface receptor complex to induce such a biological effect, and European Patent No. EP1037658B, at Example 11, proves that injection of mice with IFN-β complexed to soluble wild type IFNAR2 enhances the serum half life of IFN- β, and such activity would be useful in any disease, such as multiple sclerosis; and intrathecal administration of the type I interferon IFN- β has been demonstrated to reduce the exacerbations of multiple sclerosis. Applicants further argue that the present disclosure, provides working examples demonstrating enhanced activity of IFN- β /IFNAR2 (wild type and mutant). Applicant's arguments have been fully considered, but are not found to be persuasive.

As a first issue, Applicant is directed to the response provided above regarding the instantly claimed genus of polypeptides comprising SEQ ID NO: 2 and their unknown binding affinities for IFN- β. As a second issue, the teachings of European Patent No. EP1037658B are not commensurate with the scope of the instant claims, thus Applicant's arguments are not on point. Applicants should note that the examination of the instant claims has been limited to the scope of the elected species of "anti-viral properties" and "multiple sclerosis". As previously indicated, Figure 4, the figure merely depicts binding curves for IFN-β and IFNAR2 wild type and mutant forms and is used to extrapolate the amount of free IFN-β in the anti-viral assay. The anti-viral assay described in Example 7 is an *in vitro* assay on human amniotic cells and does not

provide any information regarding dose dependent increase in cell survival, and more importantly, provides no information with regard to immune modulatory activity. Moreover, the prior art of Hertzog et al. (of record) describe a method of regulating interferon type I functional activity by administering a soluble IFNAR2a soluble receptor (p.1, paragraph 1). Herzog also showed that soluble IFNAR2a has been found to inhibit the functional activity of type I interferon, i.e. IFN-β (p.3, first paragraph). Thus, the IFNAR2's function as a carrier of IFN-β would appear to be antagonistic to the anti-viral activity of IFN-β . Thus, the guidance provided by the instant specification is insufficient in teaching a person of ordinary skill in the art to augment IFN-β activity in autoimmune disease and multiple sclerosis. The specification is silent on the claimed composition having been administered to a patient having an autoimmune disorder or multiple sclerosis, either alone or in combination with IFN. Additionally, the instant claims are not limited to intrathecal administration.

Thus, the rejection of claims 88 and 89 is maintained for reasons of record and the discussion set forth above.

Response to Claim Rejections - 35 USC § 103

Claims 62, 66-71 and 75-76 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Piehler et al. (J. Mol. Biol. 294:223-237; 1999). The rejection set forth on pp. 8-9 of the office action dated July 26, 2006, the Advisory action dated October 17, 2006, pp. 7-9 of the office action dated July 2, 2007, and pp. 6-7 of the previous office action dated January 8, 2008 is maintained for reasons of record.

Applicants traverse the rejection, arguing that the Examiner acknowledges the unpredictability of combining two known mutations: "[i]f the outcome of the double mutation could be accurately predicted, it would not be 'interesting' to explore such a result." Further arguing that contrary to the Examiner's assertions, there is simply no suggestion in Piehler that the mutations would synergistically increase affinity for IFN-β, and that the only prediction made by Piehler is that the H78A/N100A double mutant should exhibit 20-fold tighter binding for IFN-β compared to IFN-α2. However, the affinity of the claimed double mutant was shown to be about 100 times higher than the wild type towards IFN-β. Applicant additionally argues that the

Examiner has failed to explain why the double mutant "must necessarily possess" an increased affinity for IFN-β.

Applicant's arguments have been fully considered, but are not found persuasive. With regard to Examiner's statement: "[i]f the outcome of the double mutation could be accurately predicted, it would not be 'interesting' to explore such a result.", the statement does not necessarily preclude synergism between the two mutations, because it is the amount of increase in IFN-β binding that remains to be determined, and not necessarily the presence of synergy.

Piehler et al. showed increased affinities (of twofold and fourfold respectively) for each of the separate mutations, with the N100A mutation hardly affecting the rate of IFNα2 binding. Piehler et al. further predicted a 20-fold tighter binding for IFNβ compared to IFNα2, in the IFNAR2 receptor harboring both mutations. Piehler et al. state that IFNα2 and IFN-β bind competitively to the same functional epitope (second column, p. 234), and that the N100A mutation hardly affects the binding of IFNα2, and the H78A destabilized the complex with IFNα2 only twofold (first column, p. 230); additionally stating: "Two mutations on ifnar2 (H78 and N100) result in an increased rate of dissociation (and thus higher affinity) for IFNβ but not for IFNα2." (first column, p. 234). Moreover, Piehler et al. state: "Interaction energies G^{0}_{KD} determined from single point mutations are not strictly additive, because cooperative effects are not taken into account." (first column, p. 232). Thus, that the two mutations synergistically increased binding affinity for IFN-β is not considered an unexpected result, due to the presence of cooperative effects taught by Piehler et al. As indicated in MPEP 716.02, a greater than additive effect is not necessarily sufficient to overcome a *prima facie* case of obviousness because such an effect can either be expected or unexpected. Applicants must further show that the results were greater than those which would have been expected from the prior art to an unobvious extent, and that the results are of a significant, practical advantage. *Ex parte The NutraSweet Co.*, 19 USPQ2d 1586 (Bd. Pat. App. & Inter. 1991) (Evidence showing greater than additive sweetness resulting from the claimed mixture of saccharin and L-aspartyl-L-phenylalanine was not sufficient to outweigh the evidence of obviousness because the teachings

of the prior art lead to a general expectation of greater than additive sweetening effects when using mixtures of synthetic sweeteners.).

Therefore, the rejection is maintained for reasons of record and the foregoing discussion.

Claims 77-82 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Piehler et al. (J. Mol. Biol. 294:223-237; 1999), in view of Campbell et al. (of record). The rejection set forth on pp. 8-9 of the office action dated July 26, 2006, p. 9 of the office action dated July 2, 2007 and p. 7 of the previous office action dated January 8, 2008 is maintained, for reasons of record.

Applicant disagrees with the rejection, citing the deficiency of Piehler et al. in teaching the synergistic effect of the H78A/N100A double mutant, and that Campbell does nothing to remedy the defect of Piehler. Such is not found persuasive, in view of the discussion set forth above. Therefore, the rejection is maintained for reasons of record and the foregoing commentary.

Conclusion

No claims are allowed.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR§1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to FEREYDOUN G. SAJJADI whose telephone number is (571)272-3311. The examiner can normally be reached on 6:30 AM-3:30 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Fereydoun G. Sajjadi, Ph.D.
Examiner, Art Unit 1633

/Anne Marie S. Wehbe/
Primary Examiner, Art Unit 1633